REMARKS

This is a Response to the Official Action dated January 9, 2004. After amendment of the claims as indicated above, claims 1, 47, 49-51, and 55 will remain pending in this application. Claims 48, 52-54 and 56-59 have been canceled, without prejudice, because the Examiner has indicated that they are drawn to a non-elected invention. Applicant reserves the right to file divisional applications to the non-elected subject matter.

The specification has been amended to clarify that Pluronics® "are generically known as poloxamers." The same amendment was made in the parent application (U.S. Application No. 09/075,343) where it was agreed during an interview with the Examiner that the amendment to the specification would not result in the addition of new matter to the application.

Claim 1 has been amended to further define the structure of the targeted therapeutic delivery system such that the stabilized lipid microspheres encapsulate a gas or gaseous precursor and an oil and wherein the oil further encapsulates the gas or gaseous precursor. Support for such an amendment can be found throughout the specification, for example, at Figure 2 and page 70, lines 2-3.

In view of the foregoing amendment, as well as the arguments that follow, reconsideration of the application and a notice of allowance are respectfully requested.

Summary of the Invention

The present invention, as defined by the claims, as amended herein, is directed to a targeted therapeutic delivery system for the controlled delivery of a therapeutic compound to a region of a patient. The therapeutic delivery system comprises stabilized lipid microspheres in combination with a therapeutic compound. The stabilized microspheres of the therapeutic delivery system are further defined as encapsulating a gas or gaseous precursor and an oil and wherein the oil further encapsulates the gas or gaseous precursor.

Double Patenting Rejection

Claims 1, 47, 49-51 and 55 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-102 of U.S. Patent No. 6,146,657, claims 111-173 of U.S. Patent No. 6,139,819, claim 95 of U.S. Patent No. 6,071,494, and claims 57-122 of U.S. Patent No. 6,414,139 (Office Action at 3). In making this rejection, the Office Action states that "[t]he cited patents only lack to specifically claim an oil with their compositions. However, it would have been obvious to one of ordinary skill in the art at the time of invention to further add suitable oil into the compositions of the patented claims . . ." (Office Action at 3). As explained more fully below with regard to the pending rejections under 35 U.S.C. §§ 102 and 103, the claimed targeted therapeutic delivery system that includes stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, wherein said oil further encapsulates said gas or gaseous precursor, would not have been obvious to one of ordinary skill in the art. Accordingly, it is respectfully submitted that the pending double patenting rejection is improper and should be withdrawn.

Rejections under 35 U.S.C. § 102

Grinstaff

Claims 1, 47 and 51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,498,421 to Grinstaff et al. ("Grinstaff"). The Office Action states that "Grinstaff discloses compositions comprising a biologic agent, a polymeric shell encapsulating a perfluorocarbon gas and an oil" (Office Action at 2). Applicant respectfully disagrees with this rejection, but in the interest of facilitating prosecution, Applicant has amended independent claim 1 to further recite that "said oil further encapsulates said gas or gaseous precursor" (*see* amended claim 1).

Grinstaff cannot anticipate claims 1, 47 and 51 because the reference does not disclose, explicitly or implicitly, all elements of the claimed invention. In this regard, Grinstaff teaches a "composition for in vivo delivery of a biologic, wherein said biologic is selected from: . . . a gas, optionally dispersed in a biocompatible dispersing agent, substantially completely contained within a polymeric shell . . ." (*see* Grinstaff at col. 1, line 62 – col. 8, line 17 & claim 1). Grinstaff further discloses the use of an oil as the "biocompatible dispersing agent" (*see* Grinstaff at col. 9, lines 25-32 & claim 13). As

Grinstaff indicates, however, its gas is "optionally dispersed in a biocompatible dispersing agent," or, in other words, the gas is dispersed in the oil. Because Applicant's claimed targeted therapeutic delivery system is one that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, wherein the "oil further encapsulates said gas or gaseous precursor," there can be no anticipation by Grinstaff's teaching of a gas that is "dispersed" in an oil.

For the foregoing reasons, Applicant submits that Grinstaff does not anticipate or render obvious claims 1, 47, and 51, and Applicant respectfully requests that this rejection be withdrawn.

Lanza

Claims 1, 47, and 51 also stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,989,520 to Lanza et al. ("Lanza"). The Office Action alleges, *inter alia*, that Lanza discloses "targeted therapeutic emulsions having a lipid wall which is a phospholipid, a gas therein such as perfluorinated compounds in combination with an oil and a therapeutic agent or drugs for a desired site[]" (Office Action at 5). Applicant respectfully disagrees with this rejection, but in the interest of facilitating prosecution, Applicant has amended independent claim 1 to further recite that "said oil further encapsulates said gas or gaseous precursor" (*see* amended claim 1).

Lanza cannot anticipate claims 1, 47 and 51 because the reference does not disclose, explicitly or implicitly, all elements of the claimed invention. In this regard, Lanza teaches a method for ligand-based binding of lipid encapsulated particles to molecular epitopes on a surface comprising sequentially administering (a) a site-specific ligand activated with a biotin activating agent; (b) an avidin activating agent; and (c) lipid encapsulated particles activated with a biotin activating agent, whereby the ligand is conjugated to the particles through an avidin-biotin interaction so that the resulting conjugate is bound to the molecular epitopes (*see* Lanza abstract). Perfluorcarbon emulsions may be encapsulated with the lipid particles, and the emulsions may generate gaseous vapors (*see* col. 6, lines 1 to 24, and col. 7, lines 1 to 6). Lanza further describes in its examples the use of safflower oil in its emulsions (*see, e.g.*, Example 1 of Lanza).

The encapsulated perfluorocarbon emulsions of Lanza cannot anticipate or render obvious Applicant's claimed invention since there is no teaching of a targeted therapeutic

delivery system that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, *wherein the oil further encapsulates said gas or gaseous precursor.* There is simply no teaching or suggestion in this regard and, therefore, there can be no anticipation by Lanza.

For the foregoing reasons, Applicant submits that Lanza does not anticipate or render obvious claims 1, 47, and 51, and Applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Lanza in view of Klaveness

Claims 1, 47, 51, and 55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lanza in view of U.S. Patent No. 6,261,537 to Klaveness et al. ("Klaveness").

As discussed above, Lanza fails to teach a targeted therapeutic delivery system that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, wherein the oil further encapsulates said gas or gaseous precursor. Klaveness fails to make up for this deficiency.

Klaveness is directed to "[t]argetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, having reporters comprising gas-filled microbubbles stabilised by monolayers of film-forming surfactants, the reporter being coupled or linked to at least one vector" (Klaveness at Abstract). As with Lanza, Klaveness fails to teach a targeted therapeutic delivery system that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, wherein the oil further encapsulates said gas or gaseous precursor. Accordingly, Applicant respectfully submits that the claims define patentable subject matter over the cited references, and request that the rejection under Section 103 be withdrawn.

Lanza in view of Unger

Claims 1, 47, and 49-51 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lanza in view of U.S. Patent No. 5,469,854 to Unger et al. ("Unger").

As discussed above, Lanza fails to teach a targeted therapeutic delivery system that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil,

wherein the oil further encapsulates said gas or gaseous precursor. Unger fails to make up for this deficiency.

Unger is directed to, *inter alia*, "[m]ethods of and apparatus for preparing gas-filled liposomes are described. Gas-filled liposomes prepared by these methods are particularly useful, for example, in ultrasonic imaging applications and in therapeutic drug delivery systems" (*see* Unger at Abstract). The Examiner has failed to point to a teaching in Unger of a targeted therapeutic delivery system that comprises stabilized lipid microspheres encapsulating a gas or gaseous precursor and an oil, wherein the oil further encapsulates said gas or gaseous precursor. Accordingly, Applicant respectfully submits that the claims define patentable subject matter over the cited references, and request that the rejection under Section 103 be withdrawn.

CONCLUSION

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, Applicants respectfully request allowance of all pending claims.

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